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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,820	11/25/2003	Bruce N. Ames	B00-001-4	9373

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,820	AMES ET AL.	
	Examiner	Art Unit	
	Dwayne C. Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *the response of 16FEB2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-58 are pending.

2. Claims 1-58 are rejected.

Response to Arguments

3. Applicants' arguments filed on February 16, 2006 have been fully considered but they are not persuasive. Applicants are the following points. First, applicants argue that the instant claims are drawn to pharmaceutical compositions comprising primary N-hdroxylamines, whereas the secondary N-hydroxylamines of the prior art reference of Krishna et al. are not pharmaceutical compositions. Second, applicants allege that composition claims of the claimed subject matter have a different function, namely delaying of senescence, than the composition of the prior art, which are directed to protection against oxidative damage.

4. First, applicants argue that the instant claims are drawn to pharmaceutical compositions comprising primary N-hydroxylamines, whereas the secondary N-hydroxylamines of the prior art reference of Krishna et al. are not pharmaceutical compositions. This argument is not found persuasive because of the following teachings from Krishna et al. Krishna et al. teach that "[s]table nitroxide free radicals have found a wide range of applications in biology and medicine." Krishna et al. also teach that "cellular and in vivo pharmacology of stable nitroxides and persistent spin adduct nitroxides has been investigated in detail.", (see page 5537). The skilled artisan

is provided with explicit teachings that nitroxides are known in the art of biology and medicine as well as the disclosure that it is known in the art of the pharmacology of nitroxides. In fact, Krishna et al. disclose that hydroxylamines have been shown to protect mammalian cells exposed to reactive oxygen species, such as super oxide, hydrogen peroxide, organic hydroperoxides, and redox cycling and anticancer agents, (see column 2, page 3478). Clearly, one having ordinary skill in the art could determine a dosage and pharmaceutical preparations as well as methods and modes of administration having the optimum therapeutic index because these skills are well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts and pharmaceutical preparations in order to get the maximum effect of the drug while minimizing the adverse and/or unwanted side-effects. Moreover, the administration of a pharmaceutical that is an antioxidant or a compound that possessing free-radical scavenging properties is well established in the art, and so one having ordinary skill in the art would have found it obvious to prepare pharmaceuticals of free-radical scavengers, in particular nitroxide compounds, which includes both primary and secondary N-hydroxylamines.

5. Second, applicants allege that composition claims of the claimed subject matter have a different function, namely delaying of senescence, than the composition of the prior art, which are directed to protection against oxidative damage. Accordingly, applicants further allege that the presence of a property not possessed by the prior art is evidence of nonobviousness, see MPEP 716.02(a)III. In accordance with MPEP 716.02(a)III, "The submission of evidence that a new product possesses unexpected

properties does not necessarily require a conclusion that the claimed invention is nonobvious, see *In re Payne*, 606 F.2d 303, 203, USPQ 245 (CCPA 1979). In addition, MPEP 2145 sect. III, recites that the, "[m]ere recognition of latent properties in the prior art does not render nonobviousness an otherwise known invention", see *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function "would remove from the public that which is in the public domain by virtue of its inclusion in, **or obviousness** from, the prior art.", (emphasis added) 596 F.2d at 1022, 201 USPQ 661. Furthermore, "[t]he fact that applicant has recognized another advantage which would flow naturally form following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.", *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). One having ordinary skill in the art would have been motivated to use primary N-hydroxylamines to offset the deleterious effects of reactive oxygen species to cells when the prior art specifically teaches that secondary N-hydroxylamines also perform this very same function. For this reason, the skilled artisan would expect that compounds with primary N-hydroxylamines would also reduce the effects of reactive oxygen species to cells, as well as possessing a latent property that applicant is arguing, namely delaying cellular senescence, because the only structural difference lies with the presence of absence of a hydrogen atom attached to the functional group of the N-hydroxylamine moiety. Although the prior art reference of Krishna et al. do not specifically disclose of delaying cellular senescence this latent property is an inherent feature of these hydroxyl amine containing compounds, which does not place the instant claims in a position of

nonobviousness over the prior art of Krishna et al for both the above stated and reasons of record.

Claim Objections

6. Claim 53 is objected to because of the following informalities: the last compound, di-hydroxylamine-benzylphosphate ester needs a space the phosphate and the ester. Appropriate correction is required.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krishna et al. in view of Schmidl et al. of U.S. Patent No. 5,504,072. Krishna et al. teach of the protective effects of inter alia hydroxylamines. Krishna et al. teach that

cellular damage may result from the cytotoxicity of reactive oxygen species, (see column 1, page 3477). Krishna et al. also teach that the reactive oxygen species are byproducts of normal processes in aerobic environments, and when there are imbalances in these reactive oxygen species oxidative stress results to cells, (see page 3477). Krishna et al. also disclose that hydroxylamines have been shown to protect mammalian cells exposed to reactive oxygen species, such as super oxide, hydrogen peroxide, organic hydroperoxides, and redox cycling and anticancer agents, (see column 2, page 3478). In addition, Krishna et al. teach of screening methods to test the effectiveness of hydroxylamines to provide protection to mammalian cells that are exposed to a reactive oxygen species, namely hydrogen peroxide. The results were performed with an in vitro assay, (see column 2, page 3478). In the assay model of this teaching the efficacy of the antioxidant, such as hydroxylamine, was evaluated by exposing the cells to a reactive oxygen species, namely hydrogen peroxide, and assessing the viability of the cells both in the absence and in the presence of a fixed concentration of the test compound, (see column 2, page 3480). The assessment would compare the amounts of the reactive oxygen species present, while the instant invention is comparing the amounts of the antioxidant of the hydroxylamine present after contact with the cells. There are many ways to measure the concentration of an assay, such as a decrease in the concentration of the unwanted species or compound, (as in Krishna et al.) or still by measuring the concentration of the antioxidant compound of the hydroxylamine (as is obviously claimed by applicant).

10. The instant claims differ only in screening methods for primary hydroxylamines whereas the prior art reference of Krishna et al. are directed to screening methods with the utilization of secondary amines. The skilled artisan would most certainly been motivated from the screening methods of Krishna et al. to employ other antioxidant or cytoprotective hydroxylamine compounds to protect cells from the deleterious effects due to oxidative damage due to inter alia, reactive oxygen species. The generation of reactive oxygen species, as taught by Krishna et al., is evident in many various biochemical and aerobic environments. Accordingly, if a cellular event such as from a variety of scenarios, for instance ischemia or inflammation or cancer or cytokines or still other events, which can generate and cause oxidative damage to a cell, would be obviously protected with the presence of hydroxylamine compounds, as clearly taught by Krishna et al. Clearly, it would have been obvious to the skilled artisan to utilize other hydroxylamine compounds and derivatives, which would obviously include primary hydroxylamine compounds and their derivatives, because the reaction between the oxidative damage lies between the reactive oxygen species and they hydroxylamine moiety. The skilled artisan would additionally be motivated to use primary hydroxylamine compounds and their derivatives especially since the hydroxylamine moiety of a primary hyrdroxyl amine is less sterically hindered than a primary hydroxylamine compound. In addition, one having ordinary skill in the art would have been motivated to use primary N-hydroxylamines to offset the deleterious effects of reactive oxygen species to cells when the prior art specifically teaches that secondary N-hydroxylamines also perform this very same function. For this reason, the skilled

artisan would expect that compounds with primary N-hydroxylamines would also reduce the effects of reactive oxygen species to cells because the only structural difference lies with the presence of absence of a hydrogen atom attached to the functional group of the N-hydroxylamine moiety. Moreover, the skilled artisan would even expect that the structurally related compounds of primary N-hydroxylamines would react more readily than the secondary N-hydroxylamines due to the absence of a secondary carbon-containing moiety, thus decreasing the steric hindrance of the secondary N-hydroxylamine. The amount and level of skill involved with substituting "bulky" groups, such as alkyl moieties for less "bulky" groups, such as a hydrogen atom, is well within the level of the skilled artisan. In fact, the replacement of an alkyl group for a hydrogen atom is expected and obvious, rather than as purported by applicants as unexpected and nonobvious because of the difference in steric hindrance between a primary N-hydroxylamine and a secondary N-hydroxylamine. Furthermore, one having ordinary skill in the art would have been motivated to use closely related N-hydroxylamine-containing compounds and their derivatives, which clearly embraces primary N-hydroxyl amines due to the fact that the reaction between the unwanted reactive oxygen species, is with the N-hydroxylamine-containing moiety.

Schmidl et al. teach of the pharmaceutical administration of vitamins, minerals, carbohydrates, proteins, and amino acids, and namely carnitine. Schmidl et al. teach that carnitine is to be included in nutritional compositions because it possess advantageous properties to an individual, namely improved energy metabolism, (see column 7, lines 1-21 and Table 8). "It is prima facie obvious to combine two

compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Since carnitine and nitroxide compounds are shown to have advantageous properties to an individual, the skilled artisan would be motivated to combine them together for administration.

Obviousness-type Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. The rejection of claims 1-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-57 of U.S. Patent No. 6,455,589 is obviated in view of the Terminal Disclaimer of October 17, 2005.

13. The provisional rejection of claims 1-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-57 of

copending Application No. 10/713,432 is maintained and repeated. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant invention and copending Application No. 10/713,432 teach of compositions and methods of primary N-hydroxylamine compounds and pharmaceutically acceptable salts thereof with the intended use of reducing oxidative damage or delaying senescence.

14. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Wednesdays, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, may be reached at (571) 272-0951. The official fax No. for correspondence is (571)-273-8300.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application

publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
April 6, 2006